Translation of Comparative Effectiveness of Depression Medications into Practice

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Date and Version: May 28, 2015, V12

Funding Source: Agency for Healthcare Research and Quality
Abstract

Background:
Decision aids are tools that could help translate evidence from comparative effectiveness reviews (CER) into practice by helping clinicians involve patients in making deliberate choices based on accessible information about the options available and their outcomes. Our group has developed and evaluated innovative decision aids for treatment of chronic disease in primary care practices and found that their use promoted patient involvement in choice and adherence to treatment.

Objective:
To determine the ability of decision aids to effectively translate a depression CER into practice, we have developed a literacy-sensitive depression treatment decision aid, DEPRESSION CHOICE, which adapts AHRQ’s Effective Healthcare comparative effectiveness review and associated patient guide about antidepressant medicines to satisfy the needs of clinicians, patients, and other major stakeholders. We will conduct a randomized study to estimate the effect of the decision aid on patient knowledge, patient involvement in decision making and decision-making quality, and on three and six-month measures of medication adherence and mental health, when compared with usual care.

Methods:
Approximately 300 subjects with major depression and their clinicians from a total of approximately eight to ten sites will be enrolled in this study. DEPRESSION CHOICE was developed as an educational guide to discuss medication options with patients. Clinicians will be trained in the use of the decision aid. Surveys completed by clinicians and patients will assess satisfaction with decision making and knowledge gained by patients. Follow-up surveys completed by patients will assess sustained knowledge, and information obtained directly from pharmacies will allow calculation of medication adherence. Many visits will be audio/video recorded with permission, and videos and interview transcripts will be analyzed using coding and content analysis.

Significance:
Upon completion of this research, we will have translated the Effective Healthcare CER of depression treatment into a point-of-care decision aid and will have acquired new knowledge about the effectiveness of this decision aid in primary care practices.
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1.0 SPECIFIC AIDS

AHRQ has funded the Eisenberg Center, which was established to translate the findings of comparative effectiveness research (CER) into formats that are understandable to consumers, clinicians, and policymakers. While the development of these guides by the Center provides a mechanism for disseminating CER, it is unclear whether this mechanism effectively translates the findings into real-world practice settings. We have shown that decision aids for treatment of chronic conditions that provide easily accessible information about treatment options and their outcomes facilitate knowledge transfer and greater patient involvement in usual primary care settings and may improve adherence to therapy. To our knowledge, there are no decision aids to translate the findings of the depression CER review (AHRQ 07-EHC007; Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression). Also, the impact of decision aids in priority populations, such as patients with poor health literacy, remains unclear.

To determine the ability of decision aids to effectively translate depression CER into practice, we will pursue the following specific aims:

Specific Aim #1:
To develop a literacy-sensitive depression treatment decision aid, DEPRESSION CHOICE, for use during primary care visits that will meet the needs of key stakeholders (patients and clinicians, health plans, and payers) while enabling shared decision making as a way of translating depression CER into practice. This aim has been completed, and the decision aid, DEPRESSION CHOICE, is ready to be tested in a randomized trial.

Specific Aim #2:
To obtain a preliminary estimate, in a cluster-randomized trial enrolling primary care practices serving depressed patients, of the efficacy of DEPRESSION CHOICE vs. usual care in improving measures of patient knowledge, patient involvement in decision-making and decision making quality, and 6-month measures of medication adherence and mental health.
2.0 BACKGROUND/ SIGNIFICANCE

2.1 Depression as a public health concern
With a lifetime prevalence of 17%, depression is one of the most common chronic illnesses in the U.S.\(^4\). Despite its prevalence, however, depression is often undetected and suboptimally managed. Even though primary care clinicians write 75% of antidepressant prescriptions, routine depression screening and outcomes monitoring is rare in primary care settings\(^5\). As measured by the Global Burden of Disease study, Unipolar Major Depression is the leading cause of disability worldwide\(^6\). The costs of treatment of depression are overshadowed several fold by the costs of increased healthcare utilization by depressed patients, presenteeism, absenteeism, disrupted family systems, and suicide. The annual overall economic burden of depression in the US has been estimated to have exceeded 80 billion dollars in 2000\(^1\). Practice guidelines recommend treating a patient with medications for up to one year for a first episode, up to three years for a second episode, and indefinitely for a third or later episode of depression to prevent relapse (ICSI guidelines for the treatment of major depression in adults in primary care; http://bit.ly/6t2TSZ). However, adherence rates for antidepressants are very low, with contemporary cohorts citing 6-month rates in the range of 13 to 60%\(^7\)-\(^9\), and many who are initially adherent discontinue prematurely\(^10\). Nonadherence and premature discontinuation of an antidepressant have been associated with a 77% increased risk of relapse or recurrence\(^11\) and adverse effects on disability and healthcare utilization\(^12\),\(^13\). Thus, even when patients with depression are detected and diagnosed properly, <60% will have adequate fidelity to treatment and many will suffer a protracted clinical course with great cost implications in terms of dollars and human suffering.

2.2 The Comparative Effectiveness Review on Second Generation Antidepressants
The Effective Health Care Program at AHRQ was created from the Medicare Modernization Act of 2003 (section 1013) to conduct and support studies of the outcomes and effectiveness of different treatments and to communicate findings to a variety of stakeholders (the iADAPT grants). The American Recovery and Reinvestment Act 2009 provided additional funding, including funds to support iADAPT. AHRQ’s pursuit of iADAPT stems from the need to translate this work into improved evidence-based decision making. In 2007, investigators at the Research Triangle Institute Evidence Practice Center and AHRQ released the final report on a Comparative Effectiveness review on second-generation antidepressants for adult patients with depression (AHRQ 07-EHC007). This research report has since been presented in an executive summary, a clinician guide, and two consumer guides, one in English (Figure) and another one in Spanish. This material will be the subject of our adaptation work towards creating a decision aid for use by patients and clinicians during the consultation and in follow-up to guide the selection and ongoing use of antidepressants to treat major depression.

2.3 The challenge of literacy in translating evidence into practice for patients
While ~40 million (25%) Americans lack the basic reading and computational skills necessary to fully function in our society, i.e., are functionally illiterate\(^14\), a larger percentage of 35% to 44% of English-speaking Americans\(^15\),\(^16\) have major inabilities to obtain, process and understand basic health information and services needed to make appropriate health decisions\(^17\). Low health literacy has been associated with poor health outcomes, including mental health outcomes (e.g., more depressive symptoms)\(^18\). One approach to combating low health literacy in practice is to
provide healthcare information in a format suitable for persons with limited health literacy skills. Even those with adequate health literacy skills appreciate healthcare information conveyed simply and clearly\textsuperscript{20}. Combining simple language with related graphics has been used to reinforce understanding in persons with low health literacy\textsuperscript{20-22}. However, there are unique challenges for translating evidence into practice for patients with low literacy. Specifically, these patients may not have the prose, document, and quantitative literacy skills necessary to process and understand the information provided in the Summary Guide for Antidepressant Medication (AHRQ 07-EHC007-2A). Prose literacy refers to the understanding and use of information presented as text; document literacy requires the ability to locate and use information presented in forms, tables, graphs, etc.; and quantitative literacy requires the ability to apply arithmetic operations using numbers embedded in printed materials\textsuperscript{35}. While most of the text in the Antidepressant Medication summary guide is written at an 8th grade or lower reading level, there are numerous medication names, unfamiliar terms (e.g., “bipolar disorder”) and concepts (e.g., “6 out of 10 people”) that might challenge patients with poor prose and quantitative literacy skills. The table “Research Comparing Side Effects” is likely to challenge patients’ document literacy skills and the table “Dose and Price of Antidepressants” is likely to challenge both document and quantitative literacy skills. Furthermore, patients with low literacy tend to think in concrete and immediate rather than abstract and futuristic terms\textsuperscript{20}. This tendency may make it difficult for these patients to a) critically evaluate the risks and benefits associated with antidepressant medication options, b) conceptualize potential future implications of a treatment decision, and c) understand the consequences of not adhering to a selected treatment regimen.

2.4 Use of decision aids to translate comparative effectiveness reviews into practice

Decision aids can facilitate the translation of effective interventions into practice, specifically where the benefits of the interventions clearly outweigh the harms. Allowing patients to see this balance of harms and benefits can improve their control of chronic conditions\textsuperscript{24} and can stimulate use of the beneficial options by overcoming clinical inertia while promoting adherence\textsuperscript{25}. The shared treatment decision-making model by Charles and Gafni provides a framework to understand decision aids and patient involvement in making decisions during the consultation\textsuperscript{26-28}. We have adapted this model to chronic care to inform the development and testing of our decision aids\textsuperscript{29}. According to the model, patient involvement begins with the development of a partnership and includes participation in information exchange, deliberation, and decision taking. While not all patients welcome the same level of involvement for all decisions all the time\textsuperscript{30-32} approaches that share information, which most patients say they want, while building partnership and inviting patient engagement may help patients engage to the extent they want. Once patients, even older patients with more experience in the parental mode of treatment choices, experience use of decision aids they report great interest in getting involved in similar decision making again\textsuperscript{2,3}. Decision aids can be designed to facilitate patient involvement in making decisions even among patients and clinicians with limited experience in shared decision-making\textsuperscript{33,34}. There is strong theoretical support for the use of decision aids. The shared treatment decision-making model described above identifies sharing of information as a key step in patient involvement in making decisions\textsuperscript{29}. Golin et al incorporated patient involvement in decision making into DiMatteo’s model of determinants of self-care, linking patient participation in decision-making with self-care,\textsuperscript{35} extending dominant behavioral theories (Health Belief Model, Theory of Reasoned Action, Social Cognitive Theory) that consider cognitive or normative determinants of future behavior. The shared treatment decision-making model and Golin’s
model both hinge on information exchange, as well as integration and understanding of the shared information.

Empirical results support this theoretical framework for using decision aids. The Cochrane Collaboration maintains a systematic review of randomized trials of decision aids in health care. The latest version (including studies up to December 2006) of this review included 55 trials. None of these trials evaluated depression treatment decision aids, tested the ability to implement and use decision aids in practice, or tested their effectiveness in primary care practices. The Box describes the results of these efficacy trials of decision aids versus usual care visits, pamphlets, or usual patient education.

As a result of this evolving body of evidence, patient involvement is becoming a key component of policies that seek to enhance the value of healthcare, with several national and international policy and legislative initiatives promoting and even mandating shared decision making. In the United States, the Institute of Medicine designated patient-centered health care delivery as a key feature of high quality health care, and the National Committee for Quality Assurance (NCQA) is developing health plan certification in shared decision making as a quality measure. Patient involvement in making decisions was explicitly incorporated into section 646 of the Medicare Modernization Act of 2003, and legislation promoting shared decision making and use of decision aids was enacted in the State of Washington (healthcare reform bill ESSB 5930, 2007) with similar efforts underway in Minnesota and other states.

2.5 Summary
Depression is a public health problem with adverse consequences for millions of Americans. AHRQ’s CER reviews, if translated, could improve the treatment of these patients. Decision aids can offer an accessible adaptation of CER reviews, promote patient involvement in shared decision making -- including patients with low health literacy -- and thus enhance the quality of depression care by promoting adherence to effective interventions that are consistent with patients’ values and preferences. The decision aids we have developed are for use with patients in primary care practices, and will be described in the Preliminary Work section that follows.

3.0 PRELIMINARY WORK

3.1 The Statin Choice trial
The Statin Choice one-page decision aid uses pictographs to display the 10-year coronary risk and the absolute risk reduction with statins and the potential downsides of taking statins. We conducted a 98-patient randomized trial of the Statin Choice decision aid in at-risk patients seen in a subspecialty referral practice with data collection that included in-office video recording, chart review, and post-visit patient and clinician survey. We found that immediately after the visit, patients in the decision aid group were more satisfied with the decision making process, had better understanding of the information (as tested using a knowledge questionnaire), had a calibrated sense of their risk (OR 22.4, 95% CI 5.9, 85.6) and risk reduction with statins (OR 6.7, 95% CI 2.2, 19.7), had lower decisional conflict scores and higher trust in their physician than patients receiving the control intervention. We also found that, 3 months after their visit, the odds of patients taking statins regularly was 3.4-fold greater if they had received Statin Choice (94%) vs. control (79%). Analysis of videotaped encounters during the trial showed that the
decision aid enhanced patient participation in the decision-making process and revealed that most encounters featured use of the decision aid as intended, despite minimal clinician training (about 5 minutes, prior to the first use)\textsuperscript{42}.

### 3.2 The Diabetes Medication Choice Trial

We assembled a multidisciplinary team and iteratively designed the Diabetes Medication Choice Cards decision aid to address the choice of how best to achieve glycemic control in Type 2 diabetes\textsuperscript{33}. This model of development will be similar to the one proposed in the current application insofar as it would be based on action research, include all stakeholders, be evidence-based, and use design approaches to ensure the final prototype iteration meets the needs of end users. This decision aid takes the form of cards that compare diabetes medication classes across six domains that patients and clinicians consider important in choosing among these medications\textsuperscript{45, 46}. We then conducted a clustered randomized trial to test the effectiveness of the decision aid in 11 academic primary care practices affiliated with the Mayo Clinic and Olmsted Medical Center\textsuperscript{2}, some of the same clinics that have agreed to participate in the research proposed in this application. Clinicians agreeing to participate were randomized to either use the decision aid with their eligible patients (intervention, n=21) or discuss anti-hyperglycemic medications in the usual manner (control, n=19) during a regularly scheduled clinical visit. Eligible patients were able and willing to give informed consent to participate in the trial, had type 2 diabetes for at least 1 year, had a hemoglobin A1c between 7-9.5% in the last six months, were not using insulin and were using less than four anti-hyperglycemic medications. Data sources included patient charts, patient and clinician surveys post visit, video recordings of these visits, and pharmacy records. Compared to usual care (n=37), patients randomly assigned to use the decision aid (n=48) were twice as likely (62\% vs. 31\%) to report feeling involved in the decision making process. Overall, 84\% of the clinicians considered the decision aid helpful and 90\% hoped to use the decision aid again if it were made available\textsuperscript{2}.

### 3.3 The Osteoporosis Choice Trial

With the advent of the FRAX 10-year fracture risk calculator, we were able to develop a decision aid to help patients at risk for osteoporotic fractures and their clinicians discuss bisphosphonate treatment. This decision aid was our first to include the cost of medication. To evaluate this decision aid we enrolled 100 patients of 72 clinicians at 11 primary care clinical sites affiliated with Mayo Clinic in Rochester, Minnesota, and randomized 52 patient-clinician dyads to the decision aid and 48 to the control group (five patients were lost to follow-up)\textsuperscript{47}. Compared to usual care, the decision aid was acceptable, improved knowledge, and enhanced patient involvement in decision-making. Over 70\% of clinicians thought the decision aid was helpful to convey information about fracture risk and risk reduction; the discussion when the clinician used the decision aid was 1 minute longer than the unaided one. Pharmacy data was available for all but one patient and revealed a significant improvement in the proportion of patients adherent to >80\% of prescribed bisphosphonates at 6 months with the decision aid (P= 0.03).

### 3.4 The DIAMOND Collaborative in Depression Care

The Institute for Clinical Systems Improvement (ICSI, www.icsi.org) was established in Minnesota in 1993 by HealthPartners (then Group Health), Mayo Clinic and Park Nicollet Health Services. It now comprises \textasciitilde 60 medical groups and hospitals as members and six major health plans as sponsors. It seeks to improve patient care in Minnesota through collaboration and
innovations in evidence-based medicine. In 2006, ICSI convened all major state stakeholders to pursue an improved model of care for patients with depression in primary care settings and an improved model for payment to support this model. The DIAMOND collaborative (Depression Initiative Across Minnesota, Offering a New Direction) was modeled after the IMPACT model of depression in primary care.\textsuperscript{48, 49} Payer reimbursement for this model required that participating clinics become trained and certified by ICSI to demonstrate the four IMPACT model components in their practice: (1) regular use of a valid depression measurement tool, (2) use of evidence-based guidelines, (3) development of a registry to track patients, and (4) relapse prevention training for patients who improved; to share data on relevant process issues, response and remission rates; and to enlist two new roles to hire and train: a depression care manager and a DIAMOND consulting psychiatrist. Available outcome data from this program includes process measures (no. patients screened with the Patient Health Questionnaire 9-item for depression (PHQ-9)\textsuperscript{50}, no. enrolled into care management, no. of dropouts) and outcome measures (response rate and remission rates at six months as defined by PHQ-9 scores). The availability of this model being implemented in a wide diversity of clinic settings with patients of varying economic and social backgrounds with similar outcome measures provides a unique opportunity to test the proposed adaptation of the comparative effectiveness review, a decision aid, to guide the use of second-generation antidepressants in adults with major depression.

3.5 The Development of the Depression Choice Decision Aid

Evidence, first stakeholder meeting, and encounter observations
This has been a two-pronged process: one was the synthesis of evidence regarding the risks and benefits related to the available antidepressant options, and the other was observation of clinician and patients encounters involving initiation of antidepressants in primary care practices. Regarding the first stage, it is essential for a decision aid to present the best available evidence of advantages and disadvantages related to different choices with, when pertinent, estimated probability of the outcomes.\textsuperscript{54} We used the Effective Health Care systematic review report on the comparative effectiveness of second generation antidepressants as the basis for this process (07-EHC-007)\textsuperscript{55, 56}. During the first of three stakeholder meetings led by Dr. Williams and Dr. Oftedahl, we convened psychiatrists and primary care clinicians as well as other stakeholders (ICSI, the producer of practice guidelines for the state of Minnesota and specifically of the depression guidelines used in the DIAMOND collaborative, health plans and payers) to review this document and reach agreement about it being up-to-date (specifically addressing evidence appearing since the last search (2006-2007), and revelations of publication bias in this field\textsuperscript{57}), valid, and applicable. To implement the second stage of information collection, usual clinical encounters were observed in participating DIAMOND clinics, e.g., care manager nurse or primary care clinician (MD/DO, NP/PA) discusses antidepressants.

Initial prototype development and field testing
The International Patient Decision Aid Standards (IPDAS) Collaboration, of which Dr. Montori is a member of the Steering Committee, provides recommendations and standards for the construction of decision aids.\textsuperscript{58} These standards specify key necessary content areas for evidence-based, unbiased, effective and safe decision aids and inform goals of these tools, such as how to convey to the patients the nature of the problem and the need for a decision; how to explore patient ideas, fears and expectations regarding possible decisions; how to display the
options; what information should be included; and how to check patient understanding of the options. Clinicians and patients have been instrumental in the development of prior decision aids and were critical participants in this effort as well.

As prototypes were developed and evaluated they were introduced into the clinical settings. The team evaluated the ability of the prototype to facilitate the decision making process by reviewing the content of the conversations and the quality of the conversations. The cycle of prototype developing and testing ended once the team reached consensus that the prototype was successful in involving patients in decision making and resulting in high decisional quality among target patients. The resulting prototype should satisfy minimal IPDAS criteria for a safe and unbiased decision aid. ICSI convened the second of three stakeholder meetings to seek consideration, feedback, and endorsement of the resulting tool. Final refinements included professional assessment of language and health literacy demands by experts from Mayo’s Section of Patient Education and Dr. Yost, with the aim of reducing any modifiable health literacy barriers and achieving a version consistent with plain language standards.

The patient-centered development process featured an iterative approach employing extensive field-testing. DEPRESSION CHOICE can be used by clinicians following a brief training period (4 minute video tutorial and storyboard) and has appropriate features for use at the point of care, in busy primary care practices, with patients with diverse health literacy skills. The decision aid will support patient choice among second-generation antidepressants faithfully adapting the AHRQ’s comparative effectiveness review.

4.0 RESEARCH DESIGN AND METHODS

4.1 Overview
In the first aim we developed a decision aid that translates the Comparative Effectiveness Reviews and derivate products into a decision aid for use in primary care practices by adult patients with major depression considering the start or change of an antidepressant. The second aim will be achieved with a cluster-randomized, two-group trial of primary care practices in which we will estimate the extent to which this decision aid can be used in diverse clinical settings with patients of varied literacy level to favorably impact patient knowledge, decision quality, treatment adherence, and depression outcomes.
4.2 Schema

4.3 Effectiveness of Decision Aid

4.4 STUDY SETTING AND PARTICIPANTS

4.4.1 Study Practices
This study will involve approximately 8 to 10 primary care practice sites affiliated with Mayo Clinic, Hennepin County Medical Center, and other sites in Minnesota with leadership that is willing to participate. Some of the participating practices are part of the DIAMOND collaborative.

4.4.2 Recruitment of Sites
The investigators will provide an overview of the study to personnel at each site. Investigators will call and/or visit potential practices to discuss the project in more detail. Sites that volunteer for participation will be asked to identify a lead clinician and a contact person for the study. Each practice will be provided with .5 FTE for study coordination. Prior to consenting participants, Site Study Coordinators will be trained by Central Study Staff, in areas for human subjects protections, including subject safety, data integrity, informed consent process, subject privacy and data confidentiality (see DSMP).

4.4.3 Site Requirements
The administrator of each participating site will be asked to complete a standardized practice demographic form to report data regarding race, ethnicity, and insurance status of patients seen in the practice, community size, and makeup of staff including clinicians, allied health staff, and patient educators.
The commitment requested from each site includes time (about 4 hours) for training in study procedures for site staff who will be consenting patients, including IRB certification in human subjects research, and participation in the actual conduct of the study. Other resources such as faxing and copying forms should use less than $200 in time, telephone charges and paper. Enrolled site administrator, clinician, and care manager will be asked to sign a practice agreement stating they agree to work in their practices to see that the required time and resources for participation in this study are available.

4.4.4 Study Subjects

4.4.4.1 Clinician Requirements
Prior to beginning the study, a questionnaire will be given to participating clinicians to gather the following provider demographics: type of practice, years in practice and at practice site, gender, birth year, estimate of time in direct patient care, proportion of practice devoted to patients with depression, preferred style of decision making, and average length of appointments with depression patients. All participating clinicians will also be required to sign an informed consent form.

4.4.4.2 Patient Eligibility Criteria
This study will focus on patients of participating clinicians who are likely to need to initiate drug treatment for depression, or need to intensify current treatment. Patients will be considered eligible for the study if they:

- Are an adult (≥ 18 years)
- Have a presumed diagnosis of depression (PHQ-9 ≥ 10)
- Screen negative for bipolar disorder (no prior diagnosis and/or per clinician's assessment)
- Identify their primary care clinician as their main depression provider
- Are without major barriers (i.e., severe hearing impairment, dementia, cannot communicate with the clinician in the same language) to provide written informed consent and to participate in shared decision-making (per clinician’s assessment).
- Agree to be available for follow-up survey 6 months after treatment decision.
- As judged by their clinicians: need to initiate drug treatment for depression; need to intensify current treatment by (a) increasing dosage, or (b) through the addition of a new agent.

4.4.4.3 Identification of Patient Subjects
Fliers may be posted at clinical sites, in waiting rooms and in examination rooms, and may be distributed to potentially eligible patients by clinical staff.

Study personnel will work with each of the practices to identify eligible patients from upcoming appointment schedules of the clinicians and care managers. Eligible patients who present to the practice for a depression or depression related visit will be invited to participate in the study. Sites will be encouraged to consult with schedulers, to identify patients who are requesting an appointment for symptoms potentially indicative of depression. The schedulers may be asked to state patient symptoms (e.g. fatigue, sleep disturbance, sadness, etc.) in the indications for visit, to assist in identifying potentially eligible subjects. Sites will be encouraged to consult with the
rooming nurses to formalize a process of internal referral to the site's study coordinator, should the rooming nurse identify a potentially eligible patient at the time of rooming.

Provider's schedules for upcoming patient appointments will be screened by research personnel, to identify upcoming appointments with patients. Clinical notes will be reviewed for patients with upcoming appointments to determine patients who may be potentially eligible.

4.4.4.4 Patient Enrollment
We seek to enroll 300 patient subjects in this study, comprising approximately 30-50 participants from each site. Site study coordinators, clinicians, care managers, or primary care nurses trained in human subjects research protection and study procedures will obtain written informed consent from the patients and a HIPPA-compliant release for medical records review and release of pharmacy profiles.

4.4.4.5 Patient Informed Consent Process
Study personnel may contact a potentially eligible patient via telephone, to inquire if they might be interested in considering participation (see initial telephone contact script), and if so, request they present for their scheduled appointment 10-15 minutes early.

Eligible patients will be approached by designated site personnel, while they are in an examination room awaiting their clinical visit. They will be given a flier briefly describing the study and containing a bulleted list of what the study will entail for them (presented in words and pictures/pictographs). If they would like to consider participation, the informed consent document will be reviewed with them. Once it is ensured that they have read and/or reviewed the consent document and have had all questions answered, they will indicate informed consent by signing the consent document. The informed consent document will provide permission to send surveys to the participants at their home address at 3 and 6 months following enrollment. The consent form also includes optional authorization to be audio/video recorded during the clinic encounter. Refusal to consent to this option does not exclude the patient from consenting to participate in the study.

The consent process will include signing a HIPAA-compliant authorization form to allow study personnel to obtain a pharmacy records (prescription profile for period 3 months prior to initial visit through 9 months post). If the patient does not sign the pharmacy authorization form at the clinic site, it will be mailed to them by study personnel in another attempt to obtain the necessary signature. If a patient refuses to sign the pharmacy authorization form, he/she will still be eligible for the study but will be excluded from the analysis where information about medication use is necessary (i.e. adherence).

4.5 DESCRIPTION OF INTERVENTION

4.5.1 Decision Aid Description
The decision aid, DEPRESSION MEDICATION CHOICE, uses plain language and is designed to enhance patient understanding, and satisfy IPDAS requirements for a safe and unbiased decision aid.
4.5.2 Mode of Use
Decision aids may be delivered in several ways: e.g., during the encounter by the practitioner (care manager or physician) or outside the encounter by a nurse or care manager. Our decision aids, however, are not designed for independent patient review; delivery by a clinician allows tailoring to the varying learning styles and health literacy levels of the target population for this adaptation and to the clinical and personal context of the patient. There is no strong evidence of superiority for any specific modes of use, with some evidence from our group supporting active clinician participation. We will allow the practices to choose and test their preferred approach for delivering the decision aids. We will evaluate the impact of the mode of implementation on success of implementation and required resources.

4.5.3 Training of Site Personnel
One of the design goals of the decision aid development was to minimize the need for training of those who will deliver it, in order to maximize the potential for later dissemination. The training procedures for clinicians includes a training video of <5 minutes, and a storyboard.

Central or Site Study personnel will do a demonstration in the use of the decision aid during in-person visits with participating clinics assigned to the intervention group. Central or Site Study personnel may also do a reminder of how to use the decision aid as needed or in response to deviations in the quality of delivery observed on video recordings. Brief video clips and storyboards that demonstrate the basic use of decision aid are publicly available at http://kercards.e-bm.info for clinicians to review at their convenience. Designated site staff will receive human subject protection training and will be trained to review study specific informed consent documents and obtain necessary signatures from patients.

We will request that the Mayo IRB serve as the IRB of record for Entira Family Clinics, formerly known as Family Health Services of Minnesota (FHSM). To ensure that the consenting process from Entira Family Clinics is done in accordance with regulations, the following training and oversight will occur:

- The Lead Study Coordinator will provide training to Entira Family Clinics study coordinator(s) on the consenting process, prior to enrollment of their first subject. Training will include reviewing the essential elements necessary for informed consent and simulations of the consenting process. After this training, the site study coordinator will be allowed to obtain consent from potential participants. The Lead Study Coordinator will offer further training at the Simulation Center (Mayo Clinic) where practice would include simulations of various consent scenarios.
- The central study staff will conduct a site visit to Entira Family Clinics annually (at a minimum), and as indicated.
- Site study coordinators will be encouraged to contact lead study personnel as needed. In addition to the Lead Study Coordinator, Co-PI and Program Manager also remain responsive to questions and actively monitor the study sites.
- The Lead Study Coordinator or her designee conducts biweekly/prn team meetings with site study coordinators, to assess study progress and respond to questions/concerns as needed.
- The PI, Victor Montori, MD, will have periodic meetings with participating clinicians, study coordinators, and study team.
4.5.4 Mayo Clinic Serves as Lead/Coordinating Center
The Principal Investigator (PI) has contact information for all centers (see Site Contact Information Sheet). Local sites are responsible for obtaining/maintaining study approval by their local IRBs, per local policies, and forward IRB approval letter and documents to the Mayo Clinic PI. A spreadsheet of participating sites’ documents will be reviewed and submitted to the Mayo IRB with continuing reviews (see iADAPT IRB Spreadsheet). All centers will report Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSOs) or Non-UPIRTSOs to the PI or his designee within 5 days of known event. Potential risks to patient subjects should be minimal and not of a serious nature. Any Non-UPIRTSOs will be submitted to the IRB at the time of the scheduled continuing review in a narrative format.

4.5.5 Control Group
In the course of conducting the study we will observe the educational resources that clinicians in control sites use to help patients make treatment decisions about antidepressants. Our needs assessment survey and observations in our decision aid trials in similar practices provide evidence that the use of any such material is not typical.

4.5.6 Data Collection

4.5.6.1 Patient Tracking Logs
To assess reach, we will use a tracking log to determine the rate of enrolled to invited patients in each clinic, and the characteristics of eligible patients who enrolled and declined. This will allow us to measure participation and representativeness.

4.5.6.2 Video Recordings
To assess fidelity, we will video/audio record encounters in both intervention and control groups using a compact digital video recorder with permission of all participants. We will use a checklist of elements present and absent for quantification of implementation.

Recordings are conducted using a portable digital video camera that is placed aimed at the clinician’s desk, away from the physical examination table. The clinician and the patient will be instructed on how to occlude the lens, direct the camera to a wall, or turn off the camera at any time they feel this is appropriate. Cameras containing subject identifying information will be transported in HIPAA compliant, zipper locked bags. Digital recordings are immediately uploaded to the research team’s secure server and deleted from portable devices after overnight back-up. The audio and video files are identified using a code number that does not include the name of the clinician, support staff, or patient or reference to their medical record number or date of birth. Audio and video files from facilities outside of Mayo Clinic, will be downloaded onto a password protected flash drive and forwarded to the Mayo research team via Fed Ex. On receiving the flash drives, the Mayo research team will immediately download the thumb drive to the Mayo server, where data are only accessible with password protected and logged access at the KER Unit at Mayo Clinic. The audio and video files will be kept for seven years following completion of the study and then deleted from the server.
Transcripts will be made from video/audio files. All transcriptions omit names that may have been stated during the recording, which are replaced in the transcript by purposefully false initials.

4.5.6.3 Pre-Visit Surveys
To assess patient's health literacy, they will receive a literacy evaluation tool after their written informed consent has been obtained and prior to the clinician visit.

4.5.6.4 Post-Visit Surveys
Patients will be given a questionnaire to complete at the end of the index visit to assess participant knowledge, satisfaction and decisional quality. If they are unable to complete the questionnaire immediately following the index visit, they will be provided with a self-addressed self-stamped envelope, to mail it to the coordinating center. In addition to questions related to effectiveness outcomes and health literacy, this questionnaire will also collect participants’ age and gender, race and ethnicity, marital status, years of education, occupation, household income, self-reported health and duration of depression diagnosis to describe the study cohort. Patients will also be asked if they would prefer to receive their follow-up surveys online and if so, will be asked to provide a valid e-mail address where they can be reached.

4.5.6.5 Follow-up Patient Surveys
Follow-up surveys will be e-mailed or mailed to participating patients at 3 and 6 months following the index visit. A postage-paid, addressed envelope will be included to facilitate return of the surveys. Patients who do not return the postal surveys within two weeks will be sent an e-mail reminder or mailed a second survey in an attempt to gather a response. If patients still do not return their second follow-up survey two weeks after it has been sent, an attempt will be made to deliver the survey to patients at an upcoming appointment.

The PHQ-9 assessment will be included with the 3 and 6-month surveys. The patient is asked in question #9, "Over the last 2 weeks, how often have you been bothered by "... Thoughts that you would be better off dead, or of hurting yourself in some way?" They are asked to indicate their answer by checking 0 for "not at all", 1 for "Several days", 2 for "More than half the days", and 3 for "Nearly every day." Because this assessment will be mailed by the patient directly to Mayo Clinic, and could indicate through their responses they may be at a heightened risk for suicide, a patient safety action plan will be followed (see Patient Safety Action Plan).

4.5.6.6 Patient Medical and Pharmacy Records
We will abstract patient medication changes, use and adherence to psychotherapy, mood outcomes (PHQ-9) and clinical course from the medical record, and medication use and refills from pharmacy profiles.

4.5.6.7 Future Use of Data All patients who participated in the study will be sent a letter asking their permission to use the data collected through their participation in the study for ongoing registry purposes for IRB-approved research, training and educational purposes. Non-responders will be sent a second letter to request authorization. Any non-responders to the second letter will not be used for the registry.
All data to be analyzed externally for registry purposes will be sent via Mayo Clinic approved encrypted methods (i.e. password protected flash drives and sent via Fed Ex).

4.6 OUTCOME MEASURES

4.6.1 RE-AIM Framework
Broadly, we will focus our evaluation adapting the RE-AIM framework developed specifically to assess translation of research into practice. We will address: (a) “Reach” by estimating what percent of all encounters enroll in the study and use decision aids when allocated to their use; (b) “Implementation” by assessing the fidelity which the practices are able to use the decision aid during the trial; and (c) “Effectiveness” by measuring outcomes at the level of patients and clinicians. Our approaches for addressing each are detailed in the next sections.

4.6.2 Reach and Fidelity (Implementation)
Reach will be assessed by calculating the percentage and representativeness of eligible patients who received the intervention. Patient representativeness variables for reach analyses will be based on age, sex, PHQ-9, race/ethnicity and literacy measures where available, because other data will not be available on nonparticipants. Of key importance to the validity of this trial is the ascertainment that similar patients are being enrolled at a similar rate in intervention and control groups. Fidelity will be determined by the distribution of the frequency with which checklist items were completed at each video recorded encounter, and by the proportion of uses in which >80% of items were completed.

4.6.3 PATIENT OUTCOMES (EFFECTIVENESS)

4.6.3.1 Decisional quality
A modified Decisional Conflict Scale will be used to ascertain decisional quality; the modification entails the use of brief items that explore the quality of the deliberation process during the visit. This scale, based on the Ottawa Shared Decision Making Framework, is the most commonly used validated and psychometrically known scale in decision aid trials, and one we have used in all of our investigations. Because our intent is to evaluate the impact of increased patient involvement in decision-making in the intervention and control clinics, we will use the OPTION scale. This scale assesses patient involvement in decision-making and was designed for use in reviewing recordings of primary care visits. Our group has extended the use of this tool to video recordings with excellent inter-rater reliability (intraclass correlation coefficient > 0.7). Because of the paucity of measures of patient involvement in decision making, our group has adapted this scale for self-report by patients and clinicians, an activity we have conducted in conjunction with the scale developer, Professor Glyn Elwyn. We applied this scale for the first time in the Diabetes Medication Choice trial, and found that the self-reported patient OPTION score was concordant with observed OPTION score on video recordings. Satisfaction with decision making will be assessed using items from the Decisional Conflict Scale and two specific questions that require patients to assess the extent to which they would want for themselves and recommend to others similar decision support like what they received during the visit.
4.6.3.2 Knowledge transfer
Questions have been crafted to assess knowledge about depression treatment contained in the decision aid. These questions use a response format “true / false / do not know”, and are to be answered with full access to the decision aids since they are not a test of recall, but of ‘use of information’.

4.6.3.3 Adherence to medications
Patients will identify the pharmacy or pharmacies they use to fill their prescriptions and authorize us in writing to directly obtain prescription drug data from these pharmacies. Getting data directly from the pharmacies will enable us to identify the prescription medications the subject is taking. Additionally, it will allow us to calculate medication adherence and persistence based on prescription refill behavior of the patient.

4.6.3.4 Mood outcomes
The DIAMOND project currently uses the PHQ-9 on a regular basis. The PHQ-9 ranges in scores from 1-27, where values 20-27 are considered ‘Severe Depression’. Mood response is defined as a 50% reduction in symptoms or total value as compared to baseline, using the PHQ-9. Remission is defined as a score on the PHQ-9 of less than 5. PHQ-9 responses will be measured at DIAMOND and non-DIAMOND sites at the initial visit and in the 3 and 6 month surveys.

4.6.4 Provider Outcomes (Effectiveness)
Clinician satisfaction with use of the decision aids will be measured with post-visit surveys. These are designed to be extremely brief. Visit length will be recorded at each practice by use of time stamps on video recordings and study coordinators recording time elapsed from time clinician enters/departs patient examination room.

4.7 STATISTICAL ANALYSIS

4.7.1 Analytical Plan
Jeph Herrin, PhD and Megan E. Branda, MSc will lead the statistical team for this study. All analyses will be performed on an intention-to-treat basis, and will use techniques appropriate for cluster-randomized trials.

4.7.1.1 Visit-Level Outcomes
We will analyze data through random-effects models. These statistical methods address the “unit of analysis” issue through terms for each level of grouping or clustering, and have a number of features important to this study. Specifically, these models allow for clustering within physicians and practices, and allow us to deal with repeated observations.

We will model the following outcomes at the patient level after the index visit:

(1) Decision to initiate, add, or modify drug treatment for depression: this will allow us to estimate the differences in prescription of medication for the decision aid group compared to the control group. We will conduct subgroup analyses by health literacy level to test for an interaction. We will use this test to determine whether the difference in uptake of depression
medications in the decision aid and control arms differs for the low vs. high health literacy groups.

(2) Decisional quality, satisfaction, and knowledge related to medications as measured after the encounter: through these analyses, we will evaluate the effect of decision aids on decisional quality, patient satisfaction with the encounter, and patient knowledge related to the decision.

4.7.1.2 Patient-Level Outcomes
We will model the following outcomes at the patient level using 3 and 6-month data:

(1) Antidepressant medication persistence and adherence based on decision at the index visit: Medication persistence\(^72\) will be measured as continuation of depression medications at 6-months for patients who leave the index visit with prescriptions for antidepressants - this includes their first medication and changes in the prescriptions that occur in the 6 months following the index visit. Medication adherence will be measured using fill dates from the pharmacies, measured using the Percentage of Days Covered approach\(^73, 74\).

(2) Depression outcomes: Depression treatment outcomes will be measured at baseline, at 3 and 6 months using the PHQ-9. We will estimate the proportions for treatment response (a decrease by 50% in PHQ-9 compared to baseline) and remission (PHQ-9<5).

4.7.1.3 Provider- and Practice-Level Outcomes
Finally, we will model the clinician level outcomes also using random effect models. However, for these models we will only cluster within clinic and account for the repeated measures for satisfaction and visit length while controlling clinician and practice characteristics.

4.7.2 Sample Size Estimations
Preliminary analyses of the DIAMOND database reveals that there are 8 potentially eligible patients per month per site, or ~800 potentially eligible patients available during the 12-month recruitment period. The Statin Choice cluster randomized trial evaluated the decision quality comparing the decision aid to usual care. This study reported a 9.8 point difference in decision quality\(^3\) with the standard deviation of 16.9 and 14.1 for the usual care and decision aid groups, respectively. Making the following assumptions: (1) variances are as reported in this study; (2) we seek to detect a difference of 9.8 points or greater in decision quality between two groups at significance level of 0.05, with a two-sided t-test; (3) a modest correlation of outcomes across these clinicians and practices (which is a conservative assumption) represented by an intracluster correlation coefficient (ICC = between cluster variance / total variance) of 0.05; (4) a variance inflation or design effect factor \([1 + (n−1) \cdot ICC]\), where n is the number of patients per cluster\(^75\); and (5) a ~20% attrition rate; we will have 80% power if we are able to recruit 30 patients per clinic for a total recruitment target of 240 patients. Assuming a similar ICC and attrition rate for other outcomes, this sample size will have 99% power to detect a 1 SD difference in any continuous measure (e.g., approximately a 2-point difference in a 10-question knowledge scale), and 80% power to detect a 30% difference in 6-month adherence rates assuming a control adherence rate of 50%. Actual power will be likely greater because we will adjust for baseline values and characteristics, and because of our conservative assumptions.
4.7.3 Allocation Process
Eligible participating practices will be classified by (a) the proportion of low literacy patients they see; (b) number of clinicians in the practice (< or > 2); and (c) whether the site is a DIAMOND vs. non-DIAMOND site. We will identify pairs of practices that are most similar across these parameters and randomize within each pair to intervention and control. Bias protection: The study statistical team (Dr. Herrin, Ms. Branda) will perform the randomization centrally after the practices have been enrolled, ensuring allocation concealment. This approach, however, does not offer prognostic balance at the clinician or patient levels, requiring hierarchical models to adjust for baseline differences at this level. Practices cannot be blinded to intervention or control status, but data collectors (central site personnel abstracting data from medical records) and patients providing outcomes may be unaware of their practice status. Furthermore, we will train personnel to ensure completion of study procedures, post visit surveys, and we will centrally follow patients and ensure patient surveys and pharmacy follow up is complete at 6 months to enable complete analyses according to the intention to treat principle. Randomization by practice site will prevent contamination across trial arms.

5.0 Potential Limitations
Adapting the CER reviews and patient guides to support decision making is likely to most usefully use this information to affect patient outcomes. While there is controversy about the objectives for decision aids, our group has had experience developing and testing decision aids to translate evidence into practice in a patient-centered way. These tools have improved patient understanding of the information, greater and positive involvement in treatment decision making, and in some cases improved adherence to chosen therapy. This gives us confidence in the proposed research. There is also controversy as to how to measure decisional quality, which is why we are using both established and innovative measures that reflect our conceptual approach for chronic shared treatment decision making.

Barriers to the use of decision aids in office-based primary care practice are both psychological and logistic, and these have been reviewed extensively. Clinicians may think they do not need decision support or that they prefer to take a parental approach to decision making or that choosing an antidepressant is a technical decision that is not sensitive to patient preference. Evidence from our needs assessment survey and from our decision aid trials in primary care argue strongly against this potential barrier. Patients, once enrolled, have found participation a positive experience, but patients hold similar concerns to those of clinicians as to whether patients should be participating in decision making. We will deal with this issue by two methods in the setup phase of the trial. First, we will gather and address clinicians and practice staff concerns regarding difficulties in improving depression management. Then, we will point at patient adherence as a common concern of clinicians of patients with depression and use this point of common concern to motivate clinicians’ participation in the study. For practices randomized to the intervention arm, this point can be used also to motivate them to try the decision aids, by discussing whether or not patients might become more adherent if they help select therapy using examples from the clinicians’ perspectives including recommendations with which they personally are adherent. The dissemination plan includes offering usual care sites the opportunity to use the decision aid if proven successful.
There are additional limitations associated with the randomized trial we will address to achieve Aim #2. The practices have been selected in part because of their perceived enthusiasm for the intervention, which may make results less generalizable. However, we think that in this phase of development it is appropriate to work with practices that are committed to the intervention. Also, the small number of practices, while adequate for detecting anticipated effects under somewhat mild assumptions, allows the performance at one practice, if exceptional, to drive the final results. To address this we will report summary results by practice and perform a range of sensitivity analyses to determine the robustness of any results.

5.1 Conflict of Interest
Tools under evaluation are not part of any existing effort to commercialize or profit from their use; the researchers involved in this study have not received - and will not receive with their application in this study - any royalties or other monetary benefits, directly or indirectly, from the use of the decision aids.

6.0 HUMAN SUBJECTS

6.1 Data Safety Monitoring Plan
This clinical trial has a Data Safety Monitoring Plan (see Data Safety Monitoring Plan).

6.2 Population
The participants for this study are patients with physician-diagnosis of major depression. Approximately half of the sites have patients who may be enrolled in case management of depression at participating primary care clinics in Minnesota. We plan to obtain consent from the clinicians, care managers, and any other practice members who participate in the study at each practice site. The patient subjects will also be asked to provide informed consent and to sign HIPAA forms to allow review of their medical record and for release of pharmacy profiles. Participants that will take part in procedures conducive to the completion of specific aim #2, i.e., video recordings of their consultation, will also provide consent for these procedures.

6.3 POTENTIAL RISKS

6.3.1 Clinicians and clinic staff personnel
Potential risks to clinicians (nurses, care managers) and other clinic staff members include: use of time for administering the decision aids and potential conflicts brought about by patient preferences that may contradict physician orders or usual practices. These issues will be addressed in the initial training and follow-up training sessions.

6.3.2 Patient
Potential risks to patient subjects should be minimal. They will receive either usual care or care informed by the decision aid tools. The intervention is an educational tool for use during the clinic visit to help patients make decisions about depression medications. The tool does not make recommendations or result in prescriptions without the participation of the clinician, and the tool is not to be used outside a clinical visit in which a clinician can place the information in context.
The completion of the surveys should require no more than 20 minutes. People can stop study participation at any time. The patient will understand that the surveys are not confidential and may be seen by study personnel outside the clinic where they receive care. The time spent filling out the surveys should be the biggest inconvenience.

6.4 PROTECTION AND CONFIDENTIALITY

6.4.1 Subject Confidentiality
Confidentiality risks will be minimized by using study numbers on surveys and keeping the list linking the study numbers and subjects’ names in a locked file cabinet. The linking list will be destroyed at the end of the study. Review of medical records could result in risks to confidentiality. Data transfer between clinics and the central office will occur in person, by Fed Ex, or when pertinent using a study-secure fax.

The electronic data will be stored in the REDCap (Research Electronic Data Capture) application. REDCap will also be utilized for 3 and 6 month patient electronic surveys. REDCap is a standalone system with no interaction or connectivity to other systems, and it is located behind the Mayo Clinic firewall. The application contains multiple levels of authentication and access controls. Users must use a Mayo Clinic LAN ID/password to connect to REDCap and their ID must be specifically authorized in order to access an individual study's data.

All changes to the data, and each "record viewed" is logged back to the individual LAN ID with a time stamp. When the case report forms are configured, each field has an attribute that can be set to flag it as an “identifier”. This “identifier” is used by REDCap to control certain actions related to the field.

REDCap also has several built in functions to control the exporting of identifying information. Individual users are each granted specific export rights, including – None, De-Identified, and Full. Additional export de-identification options include removing identifiers and dates, hashing IDs and date shifting.

All external collaboration goes through a separate server managed by the Research Computing Facility. External users are individually authorized to the portal and specifically assigned to a study. Within a study, users at a site can be assigned to Data Access Groups, so they do not have any rights to data from other Data Access Groups. Otherwise, all the same logging and security measures apply.

The data can be accessed by the statistical team at any time and downloaded into a statistical software package. The statistical team will review the data on a monthly basis to ensure data accuracy and completeness. All data, documents, and analysis findings will be housed within the Mayo Clinic system that is password protected and backed up on a nightly basis. The data will be stored within the secure system for seven years following completion of the study.

6.4.2 Data Management
Confidentiality risks will be minimized by not including names on field notes or transcribed recordings. All study data (even though none of it will include names of any subjects) will be kept in locked file cabinets or password-protected secure servers to which only authorized
personnel from the Knowledge and Encounter Research Unit at Mayo Clinic have access. These servers are within the ultra-secure facility that operates Mayo Clinic information technology infrastructure.

6.4.3 Video and Audio Recordings
Cameras, audio files containing subject identifying information will be transported in HIPAA compliant, zipper locked bags. Transfer of study files will occur in person, through secure fax, or by Fed Ex.

Visit video recordings will be kept in a password-protected server-level files until seven years following completion of the study. We plan to video record visits to ascertain the fidelity with which clinicians use the decision aid. We have video recorded patient visits in our efficacy trials, a procedure approved by the Mayo IRB. These recordings are conducted using a portable digital video camera. The clinician and the patient will be instructed on how to redirect the lens or turn off the camera at any time they feel this is appropriate. The video recordings are kept in electronic format in the hard drive of the camera, until they are transferred the same day to secure, firewalled, research servers with limited password-protected access. These video files are identified using a unique identifier that does not include the name of the clinician, staff, or patient or reference to their medical record number or date of birth. These videos are only accessible at a workstation, with password protected and logged access, at the Knowledge and Encounter Research Unit at Mayo Clinic, where all the analyses will be conducted.

6.5 Inclusion of Women and Minorities

6.5.1 Clinicians and clinic staff personnel as subjects
This is a study of clinicians (primary care physicians, nurses, care managers) and their patients. The practices include both men and women clinicians, although the majority of care managers are women and about 25% of physicians are female. Clinics participating in DIAMOND have staff members who are of racial or ethnic heritage other than Caucasian. The staff make up is not known entirely but does include Native American, Hispanic and African-American individuals.

6.5.2 Patients as subjects
This is a study of all patients 18 years and older who are depressed and are receiving care in participating clinics. We will make every effort to enroll minority patients, and we expect to have adequate enrollment of patients of all genders. Patient logs enable the central office and the study PI and statisticians to monitor the enrollment distributions and, through audit and feedback, help participating sites reach target enrollment figures that will enhance the representativeness and applicability of study results.
7.0 Literature Cited


